ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Targretin 75 mg capsules, soft

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 75 mg of bexarotene
For excipients, see 6.1

3. PHARMACEUTICAL FORM

Soft capsule

Off-white capsule, containing a liquid suspension and imprinted with “Targretin”

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Targretin capsules are indicated for the treatment of skin manifestations of advanced stage CTCL patients refractory to at least one systemic treatment.

4.2 Posology and method of administration

Bexarotene therapy should only be initiated and maintained by physicians experienced in the treatment of patients with CTCL. The recommended initial dose is 300 mg/m^2/day. Targretin capsules should be taken as a single oral daily dose with a meal (see 4.5). Initial dose calculations according to body surface area are as follows:

Initial dose level (300 mg/m^2/day)		Number of 75 mg Targretin capsules
Body Surface Area (m^2)	Total daily dose (mg/day)	
0.88 – 1.12	300	4
1.13 - 1.37	375	5
1.38 - 1.62	450	6
1.63 - 1.87	525	7
1.88 - 2.12	600	8
2.13 - 2.37	675	9
2.38 - 2.62	750	10

Dose modification guidelines: the 300 mg/m^2/day dose level may be adjusted to 200 mg/m^2/day then to 100 mg/m^2/day, or temporarily suspended, if necessitated by toxicity. When toxicity is controlled, doses may be carefully readjusted upward. With appropriate clinical monitoring, individual patients may benefit from doses above 300 mg/m^2/day. Doses greater than 650 mg/m^2/day have not been evaluated in patients with CTCL. In clinical trials, bexarotene was administered for up to 118 weeks to patients with CTCL. Treatment should be continued as long as the patient is deriving benefit.
Use in children and adolescents: the clinical safety and effectiveness of bexarotene in the paediatric population (below 18 years of age) have not been studied and this product should not be used in a paediatric population until further data become available.

Use in the elderly: of the total number of patients with CTCL in clinical studies, 61% were 60 years or older, while 30% were 70 years or older. No overall differences in safety were observed between patients 70 years or older and younger patients, but greater sensitivity of some older individuals to bexarotene cannot be ruled out. The standard dose should be used in the elderly.
Renal insufficiency: no formal studies have been conducted in patients with renal insufficiency. Clinical pharmacokinetic data indicate that urinary elimination of bexarotene and its metabolites is a minor excretory pathway for bexarotene. In all evaluated patients, the estimated renal clearance of bexarotene was less than 1 ml/minute. In view of the limited data, patients with renal insufficiency should be monitored carefully while on bexarotene therapy.

4.3 Contraindications

Known hypersensitivity to bexarotene or to any of the excipients of the product
Pregnancy and lactation
Women of child-bearing potential without effective birth-control measures
History of pancreatitis
Uncontrolled hypercholesterolaemia
Uncontrolled hypertriglyceridaemia
Hypervitaminosis A
Uncontrolled thyroid disease
Hepatic insufficiency
Ongoing systemic infection

4.4 Special warnings and special precautions for use

General: Targretin capsules should be used with caution in patients with a known hypersensitivity to retinoids. No clinical instances of cross-reactivity have been noted. Patients receiving bexarotene should not donate blood for transfusion.
Lipids: hyperlipidaemia has been identified as an effect associated with the use of bexarotene in clinical studies. Fasting blood lipid determinations (triglycerides and cholesterol) should be performed before bexarotene therapy is initiated and at weekly intervals until the lipid response to bexarotene is established, which usually occurs within two to four weeks, and then at intervals no less than monthly thereafter. Fasting triglycerides should be normal or normalised with appropriate intervention prior to bexarotene therapy. Every attempt should be made to maintain triglyceride levels below 4.52 mmol/l in order to reduce the risk of clinical sequelae. If fasting triglycerides are elevated or become elevated during treatment, institution of antilipaemic therapy is recommended, and if necessary, dose reductions (from 300 mg/m^2/day of bexarotene to 200 mg/m^2/day, and if necessary to 100 mg/m^2/day) or treatment discontinuation. Data from clinical studies indicate that bexarotene concentrations were not affected by concomitant administration of atorvastatin. However, concomitant administration of gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene and therefore, concomitant administration of gemfibrozil with bexarotene is not recommended (see 4.5). Elevations of serum cholesterol should be managed according to current medical practice.

Pancreatitis: acute pancreatitis associated with elevations of fasting serum triglycerides has been reported in clinical studies. Patients with CTCL having risk factors for pancreatitis (e.g., prior episodes of pancreatitis, uncontrolled hyperlipidaemia, excessive alcohol consumption, uncontrolled diabetes mellitus, biliary tract disease, and medications known to increase triglyceride levels or to be associated with pancreatic toxicity) should not be treated with bexarotene, unless the potential benefit outweighs the risk.

Liver Function Test (LFT) abnormalities: LFT elevations associated with the use of bexarotene have been reported. Based on data from ongoing clinical trials, elevation of LFTs resolved within one month in 80% of patients following a decrease in dose or discontinuation of therapy. Baseline LFTs should be obtained, and LFTs should be carefully monitored weekly during the first month and then monthly thereafter. Consideration should be given to a suspension or discontinuation of bexarotene if test results reach greater than three times the upper limit of normal values for SGOT/AST, SGPT/ALT, or bilirubin.

Thyroid function test alterations: changes in thyroid function tests have been observed in patients receiving bexarotene, most often noted as a reversible reduction in thyroid hormone (total thyroxine [total T_4]) and thyroid-stimulating hormone (TSH) levels. Baseline thyroid function tests should be obtained and then monitored at least monthly during treatment and as indicated by the emergence of symptoms consistent with hypothyroidism. Patients with symptomatic hypothyroidism on bexarotene therapy have been treated with thyroid hormone supplements with resolution of symptoms.

Leucopenia: leucopenia associated with bexarotene therapy has been reported in clinical studies. The majority of cases resolved after dose reduction or discontinuation of treatment. Determination of white blood cell count with differential count should be obtained at baseline, weekly during the first month and then monthly thereafter.

Anaemia: anaemia associated with bexarotene therapy has been reported in clinical studies. Determination of haemoglobin should be obtained at baseline, weekly during the first month and then monthly thereafter. Decreases of haemoglobin should be managed according to current medical practice.

Lens opacities: following bexarotene treatment, some patients were observed to have previously undetected lens opacities or a change in pre-existing lens opacities unrelated to treatment duration or dose level of exposure. Given the high prevalence and natural rate of cataract formation in the older patient population represented in the clinical studies, there was no apparent association between the incidence of lens opacity formation and bexarotene administration. However, an adverse effect of long-term bexarotene treatment on lens opacity formation in humans has not been excluded. Any patient treated with bexarotene who experiences visual difficulties should have an appropriate ophthalmologic examination.

Vitamin A supplementation: because of the relationship of bexarotene to vitamin A, patients should be advised to limit vitamin A supplements to ≤15,000 IU/day to avoid potential additive toxic effects.

Patients with diabetes mellitus: caution should be exercised when administering bexarotene in patients using insulin, agents enhancing insulin secretion (e.g. sulfonylureas), or insulin-sensitisers (e.g. thiazolidinediones). Based on the known mechanism of action, bexarotene may potentially enhance the action of these agents, resulting in hypoglycaemia. No cases of hypoglycaemia associated with the use of bexarotene as monotherapy have been reported.

Photosensitivity: the use of some retinoids has been associated with photosensitivity. Patients should be advised to minimise exposure to sunlight and avoid sun lamps during therapy with bexarotene, as *in vitro* data indicate that bexarotene may potentially have a photosensitising effect.

Oral contraceptives: bexarotene can potentially induce metabolic enzymes and thereby theoretically reduce the efficacy of oestroprogestive contraceptives. Thus, if treatment with bexarotene is intended in a woman of child-bearing potential, a reliable, non-hormonal form of contraception is also required, because bexarotene belongs to a therapeutic class for which the human malformative risk is high.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions: effects of other substances on bexarotene: no formal studies to evaluate drug interactions with bexarotene have been conducted. On the basis of the oxidative metabolism of bexarotene by cytochrome P450 3A4 (CYP3A4), coadministration with other CYP3A4 substrates such as ketoconazole, itraconazole, protease inhibitors, clarithromycin and erythromycin may theoretically lead to an increase in plasma bexarotene concentrations. Furthermore, co-administration with CYP3A4 inducers such as rifampicin, phenytoin, dexamethasone or phenobarbital may theoretically cause a reduction in plasma bexarotene concentrations.

A population analysis of plasma bexarotene concentrations in patients with CTCL indicated that concomitant administration of gemfibrozil resulted in substantial increases in plasma concentrations of

bexarotene. The mechanism of this interaction is unknown. Under similar conditions, bexarotene concentrations were not affected by concomitant administration of atorvastatin or levothyroxine. Concomitant administration of gemfibrozil with bexarotene is not recommended.

Drug interactions: effects of bexarotene on other substances: there are indications that bexarotene may induce CYP3A4. Therefore, repeated administration of bexarotene may result in an auto-induction of its own metabolism and, particularly at dose levels greater than 300 mg/m^2/day, may increase the rate of metabolism and reduce plasma concentrations of other substances metabolised by cytochrome P450 3A4, such as tamoxifen. For example bexarotene may reduce the efficacy of oral contraceptives (see 4.4 and 4.6).

Laboratory test interactions: CA125 assay values in patients with ovarian cancer may be accentuated with bexarotene therapy.

Food interactions: in all clinical trials, patients were instructed to take Targretin capsules with or immediately following a meal. In one clinical study, plasma bexarotene AUC and C_{max} values were substantially higher following the administration of a fat-containing meal versus those following the administration of a glucose solution. Because safety and efficacy data from clinical trials are based upon administration with food, it is recommended that Targretin capsules be administered with food.

On the basis of the oxidative metabolism of bexarotene by cytochrome P450 3A4, grapefruit juice may theoretically lead to an increase in plasma bexarotene concentrations.

4.6 Pregnancy and lactation

Pregnancy: there are no adequate data from the use of bexarotene in pregnant women. Studies in animals have shown reproductive toxicity. Based on the comparison of animal and patient exposures to bexarotene, a margin of safety for human teratogenicity has not been demonstrated (see 5.3). Bexarotene is contraindicated in pregnancy (see 4.3).

If this drug is used inadvertently during pregnancy, or if the patient becomes pregnant while taking this medicinal product, the patient should be informed of the potential hazard to the foetus.

Women of childbearing potential must use adequate birth-control measures when bexarotene is used. A negative, sensitive, pregnancy test (e.g. serum beta-human chorionic gonadotropin, beta-HCG) should be obtained within one week prior to bexarotene therapy. Effective contraception must be used from the time of the negative pregnancy test through the initiation of therapy, during therapy and for at least one month following discontinuation of therapy. Whenever contraception is required, it is recommended that two reliable forms of contraception be used simultaneously. Bexarotene can potentially induce metabolic enzymes and thereby theoretically reduce the efficacy of oestroprogestative contraceptives (see 4.5). Thus, if treatment with bexarotene is intended in a woman with child-bearing potential, a reliable, non-hormonal contraceptive method is also recommended. Male patients with sexual partners who are pregnant, possibly pregnant, or may potentially become pregnant must use condoms during sexual intercourse while taking bexarotene and for at least one month after the last dose.

Lactation: it is not known whether bexarotene is excreted in human milk. Bexarotene should not be used in nursing mothers.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, dizziness and visual difficulties have been reported in patients taking Targretin. Patients who experience dizziness or visual difficulties during therapy must not drive or operate machinery.

4.8 Undesirable effects

The safety of bexarotene has been examined in clinical studies of 193 patients with CTCL who received bexarotene for up to 118 weeks and in 420 non-CTCL cancer patients in other studies.

In 109 patients with CTCL treated at an initial dose of 300 mg/m^2/day, the most commonly reported adverse drug reactions were hyperlipaemia ((primarily elevated triglycerides) 74%), hypothyroidism (29%), hypercholesterolaemia (28%), headache (27%), leucopenia (20%), pruritus (20%), asthenia (19%), rash (16%), exfoliative dermatitis (15%), and pain (12%).

The following drug-related adverse reactions were reported during clinical studies in patients with CTCL (N=109) treated at an initial dose of 300 mg/m^2/day. The frequency of adverse reactions are classified as very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), and very rare (<1/10,000).

Haemic & Lymphatic

Very common:	leucopenia
Common:	hypochromic anaemia, lymphadenopathy, lymphoma like reaction
Uncommon:	anaemia, blood dyscrasia, coagulation disorder, increased coagulation time, eosinophilia, leukocytosis, lymphocytosis, purpura, thrombocythaemia, thrombocytopenia

Endocrine

Very common:	hypothyroidism
Common:	thyroid disorder
Uncommon:	hyperthyroidism

Metabolic & Nutrition

Very common:	hyperlipaemia, hypercholesterolaemia
Common:	increased SGOT, increased SGPT, increased lactic dehydrogenase, increased creatinine, hypoproteinaemia, weight gain
Uncommon:	bilirubinaemia, increased blood urea nitrogen, gout, decreased High Density Lipoprotein

Nervous system

Common:	insomnia, dizziness, hypesthesia
Uncommon:	agitation, ataxia, depression, hyperaesthesia, neuropathy, vertigo

Special senses

Common:	dry eyes, deafness, eye disorder
Uncommon:	abnormal vision, amblyopia, blepharitis, specified cataract, conjunctivitis, corneal lesion, ear disorder, visual field defect

Cardiovascular

Common:	peripheral oedema
Uncommon:	oedema, hemorrhage, hypertension, tachycardia, varicose vein, vasodilatation

Digestive

Common:	nausea, diarrhoea, dry mouth, cheilitis, anorexia,constipation, flatulence, abnormal liver function tests, vomiting
Uncommon:	gastrointestinal disorder, hepatic failure, pancreatitis

Skin & appendages

Very common:	pruritus, rash, exfoliative dermatitis
Common:	dry skin, skin disorder, alopecia, skin ulcer, acne, skin hypertrophy, skin nodule, sweating
Uncommon:	hair disorder, herpes simplex, nail disorder, pustular rash, serous drainage, skin discoloration

Musculoskeletal

Common:	arthralgia, bone pain, myalgia
Uncommon:	myasthenia

Urogenital

Uncommon:	albuminuria, abnormal kidney function

Body as a whole

Very common:	headache, asthenia, pain
Common:	altered hormone level, chills, abdominal pain, allergic reaction, infection
Uncommon:	back pain, cellulitis, fever, parasitic infection, abnormal lab test, mucous membrane disorder, neoplasm

The following adverse reactions were noted with increased frequency when bexarotene was administered at a dose >300 mg/m^2/day (CTCL): anaemia, hypochromic anaemia, eosinophilia, bilirubinaemia, increased blood urea nitrogen, depression, abnormal vision, specified cataract, vasodilatation, diarrhoea, anorexia, pancreatitis, gastrointestinal disorder, alopecia, serous drainage, hair disorder, nail disorder, myasthenia, albuminuria, chills, altered hormone level, back pain and fever.

Additional adverse reactions were also noted when bexarotene was administered at a dose >300 mg/m^2/day (CTCL): abnormal white blood cells, increased gonadotrophic luteinizing hormone, weight loss, increased alkaline phosphatase, increased creatinine phosphokinase, somnolence, hypertonia, decreased libido, nervousness, lacrimation disorder, night blindness, tinnitus, dyspnoea, sinusitis, dyspepsia, maculopapular rash and flu syndrome.

In non-CTCL cancer patients the following adverse reactions were noted with increased frequency when bexarotene was administered at a dose of 300 mg/m^2/day: anaemia, increased coagulation time, leucocytosis, depression, abnormal vision, specified cataract, vasodilatation, cheilitis, dry mouth, dry skin, back pain and fever. The following additional reactions were also noted: paraesthesia, dyspnoea, pharyngitis, thirst, maculopapular rash and chest pain.

In non-CTCL cancer patients the following adverse reactions were noted with increased frequency when bexarotene was administered at a dose of >300 mg/m^2/day (compared to administration to CTCL patients at 300 mg/m^2/day): anaemia, increased coagulation time, thrombocytopenia, bilirubinaemia, depression, amblyopia, abnormal vision, specified cataract, conjunctivitis, vasodilatation, oedema, nausea, diarrhoea, dry mouth, pancreatitis, dry skin, nail disorder, skin discolouration, albuminuria, fever, back pain and mucous membrane disorder.

The following additional adverse reactions were also noted in non-CTCL cancer patients when bexarotene was administered at a dose >300 mg/m^2/day: decreased thromboplastin, ecchymosis, abnormal erythrocytes, petechia, abnormal white blood cells, increased alkaline phosphatase, weight loss, hypercalcaemia, increased creatine phosphokinase, increased lipase, dehydration, anxiety, confusion, paraesthesia, peripheral neuritis, nystagmus, nervousness, somnolence, emotional lability, taste perversion, migraine, arrhythmia, peripheral vascular disorder, dyspnoea, increased cough, haemoptysis, pharyngitis, mouth ulceration, stomatitis, abnormal stools, dyspepsia, dysphagia, eructation, oral moniliasis, maculopapular rash, vesicobullous rash, leg cramps, haematuria, chest pain, pelvic pain, body odour and generalised oedema.

At doses of 300 mg/m^2/day (non-CTCL) there were also isolated reports (single patient reports) of the following: abnormal white blood cells, increased creatine phosphokinase, hyponatraemia, weight loss, circumoral paraesthesia, taste perversion, palpitation, epistaxis, pneumonia, respiratory disorder, abnormal stools, dyspepsia, increased appetite, psoriasis and carcinoma.

With increased dosage (>300 mg/m^2/day, CTCL and non-CTCL), there were also isolated reports (single patient reports) of the following: bone marrow depression, decreased prothrombin, decreased gonadotrophic luteinizing hormone, dehydration, hypokalaemia, increased amylase, hyperuricaemia,

hypocholesterolaemia, hypolipaemia, hypomagnesaemia, hyponatraemia, hypovolaemia, abnormal gait, confusion, stupor, abnormal thinking, decreased libido, subdural haematoma, taste perversion, eye pain, congestive heart failure, pallor, vascular anomaly, vascular disorder, laryngismus, pneumonia, rhinitis, lung disorder, pleural disorder, cholestatic jaundice, abnormal stools, dysphagia, eructation, jaundice, liver damage, cholecystitis, gingivitis, melaena, nausea and vomiting, tenesmus, thirst, herpes zoster, seborrhoea, contact dermatitis, furunculosis, lichenoid dermatitis, arthritis, joint disorder, leg cramps, polyuria, breast enlargement, impotence, nocturia, urinary retention, impaired urination, urine abnormality, malaise, viral infection, chest pain, generalized oedema, enlarged abdomen, face oedema and photosensitivity reaction.

The majority of adverse reactions were noted at a higher incidence at doses greater than 300 mg/m^2/day. Generally, these resolved without sequelae on dose reduction or drug withdrawal. However, among a total of 810 patients including those without malignancy treated with bexarotene, there were three serious adverse reactions with fatal outcome (acute pancreatitis, subdural haematoma and liver failure). Of these, liver failure, subsequently determined to be not related to bexarotene, was the only one to occur in a CTCL patient.

Hypothyroidism generally occurs 4-8 weeks after commencement of therapy. It may be asymptomatic and responds to treatment with thyroxine and resolves upon drug withdrawal.

Bexarotene has a different adverse reaction profile to other oral, non-retinoid X receptor (RXR) - selective retinoid drugs. Owing to its primarily RXR-binding activity, bexarotene is less likely to cause mucocutaneous, nail, and hair toxicities; arthralgia; and myalgia; which are frequently reported with retinoic acid receptor (RAR) -binding agents.

4.9 Overdose

No clinical experience with an overdose of Targretin capsules has been reported. Any overdose should be treated with supportive care for the signs and symptoms exhibited by the patient.

Doses up to 1000 mg/m^2/day of bexarotene have been administered in clinical studies with no acute toxic effects. Single doses of 1500 mg/kg (9000 mg/m^2) and 720 mg/kg (14,400 mg/m^2) were tolerated without significant toxicity in rats and dogs, respectively.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: other antineoplastic agents ATC code: L01XX25

Bexarotene is a synthetic compound that exerts its biological action through selective binding and activation of the three RXRs: α, β, and γ. Once activated, these receptors function as transcription factors that regulate processes such as cellular differentiation and proliferation, apoptosis, and insulin sensitisation. The ability of the RXRs to form heterodimers with various receptor partners that are important in cellular function and in physiology indicates that the biological activities of bexarotene are more diverse than those of compounds that activate the RARs. *In vitro,* bexarotene inhibits the growth of tumour cell lines of haematopoietic and squamous cell origin. *In vivo*, bexarotene causes tumour regression in some animal models and prevents tumour induction in others. However, the exact mechanism of action of bexarotene in the treatment of cutaneous T-cell lymphoma (CTCL) is unknown.

Bexarotene capsules were evaluated in clinical trials of 193 patients with CTCL of whom 93 had advanced stage disease refractory to prior systemic therapy. Among the 61 patients treated at an initial dose of 300 mg/m^2/day, the overall response rate, according to a global assessment by the physician, was 51% (31/61) with a clinical complete response rate of 3%. Responses were also determined by a composite score of five clinical signs (surface area, erythema, plaque elevation, scaling and

hypo/hyperpigmentation) which also considered all extracutaneous CTCL manifestations. The overall response rate according to this composite assessment was 31% (19/61) with a clinical complete response rate of 7% (4/61).

5.2 Pharmacokinetic properties

Absorption/dose proportionality: pharmacokinetics were linear up to a dose of 650 mg/m^2. Terminal elimination half-life values were generally between one and three hours. Following repeat once daily dose administration at dose levels ≥ 230 mg/m^2, C_{max} and AUC in some patients were less than respective single dose values. No evidence of prolonged accumulation was observed. At the recommended initial daily-dose level (300 mg/m^2), single-dose and repeated daily-dose bexarotene pharmacokinetic parameters were similar.

Protein binding/distribution: bexarotene is highly bound (>99%) to plasma proteins. The uptake of bexarotene by organs or tissues has not been evaluated.

Metabolism: bexarotene metabolites in plasma include 6- and 7-hydroxy-bexarotene and 6- and 7-oxo-bexarotene. *In vitro* studies suggest glucuronidation as a metabolic pathway, and that cytochrome P450 3A4 is the major cytochrome P450 isozyme responsible for formation of the oxidative metabolites. Based on the *in vitro* binding and the retinoid receptor activation profile of the metabolites, and on the relative amounts of individual metabolites in plasma, the metabolites have little impact on the pharmacological profile of retinoid receptor activation by bexarotene.

Excretion: neither bexarotene nor its metabolites are excreted in urine in any appreciable amounts. The estimated renal clearance of bexarotene is less than 1 ml/minute. Renal excretion is not a significant elimination pathway for bexarotene.

5.3 Preclinical safety data

Carcinogenesis, mutagenesis, impairment of fertility: bexarotene is not genotoxic. Carcinogenicity studies have not been conducted. Fertility studies have not been conducted; however, in sexually immature male dogs, reversible aspermatogenesis (28-day study) and testicular degeneration (91-day study) were seen. When bexarotene was administered for six months to sexually mature dogs, no testicular effects were seen. Effects on fertility cannot be excluded. Bexarotene, in common with the majority of retinoids, was teratogenic and embryotoxic in an animal test species at systemic exposures that are achievable clinically in humans. Irreversible cataracts involving the posterior area of the lens occurred in rats and dogs treated with bexarotene at systemic exposures that are achievable clinically in humans. The aetiology of this finding is unknown. An adverse effect of long-term bexarotene treatment on cataract formation in humans has not been excluded.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
macrogol
polysorbate
povidone
butylated hydroxyanisole

Capsule shell:
gelatin
sorbitol special-glycerin blend (glycerin, sorbitol, sorbitol anhydrides (1,4-sorbitan), mannitol and water)
titanium dioxide (E171)

printing ink (shellac glaze-45% (20% esterified) in SD-45 alcohol, indigo carmine lake (E132) and simethicone)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.
Keep the bottle tightly closed.

6.5 Nature and contents of container

High-density polyethylene bottles with child-resistant closures containing 100 capsules

6.6 Instructions for use and handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

Ligand Pharmaceuticals UK Limited
Innovis House
108 High Street
Crawley
West Sussex
RH10 1BB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/178/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 March 2001

10. DATE OF REVISION OF THE TEXT

11/06/02

ANNEX II

ANNEX III

LABELLING AND PACKAGE LEAFLET

B. PACKAGE LEAFLET

PACKAGE LEAFLET

TARGRETIN 75 mg Capsules, soft
(Bexarotene)

READ ALL OF THIS LEAFLET CAREFULLY BEFORE YOU START TAKING THIS MEDICINE.

- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

1. What Targretin is and what it is used for
2. Before you take Targretin
3. How to take Targretin
4. Possible side effects
5. Storing Targretin
6. Further Information

Name of medicinal product
Targretin 75 mg Capsules,soft
Bexarotene

Active substance and other ingredients
Targretin is available as soft capsules for oral use in a white plastic bottle containing 100 capsules. Each Targretin capsule contains 75 mg of the active substance bexarotene. The capsules also contain the other ingredients macrogol, polysorbate, povidone and butylated hydroxyanisole.

The capsule shell consists of gelatin, sorbitol special-glycerine blend (glycerin, sorbitol, sorbitol anhydrides (1,4-sorbitan), mannitol and water), titanium dioxide (E171) and printing ink (shellac glaze-45% (20% esterified) in SD-45 alcohol, indigo carmine lake (E132) and simethicone).

Marketing Authorisation Holder
Ligand Pharmaceuticals UK Limited
Innovis House
108 High Street
Crawley
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Manufacturer
Galen Limited
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Craigavon
BT63 5UA
United Kingdom

1. WHAT TARGRETIN IS AND WHAT IT IS USED FOR

The active substance in Targretin, bexarotene, belongs to a group of medicines known as retinoids, which are related to vitamin A. Targretin capsules are used by patients with advanced stage cutaneous

T-cell lymphoma (CTCL) whose disease has not responded to other therapies. CTCL is a condition in which certain cells of the body's lymph system called T-lymphocytes become cancerous and affect the skin.

2. BEFORE YOU TAKE TARGRETIN

Do not take Targretin:
- if you know that you are allergic to bexarotene or to any of the other ingredients.
- if you are pregnant or breast feeding or if you can become pregnant and are not using effective birth control measures.
- if you have a history of pancreatitis, have uncontrolled lipid (blood fats) elevations (high blood cholesterol or high blood triglycerides), have a condition known as hypervitaminosis A, have uncontrolled thyroid disease, have insufficient liver function or have an ongoing systemic infection.

Take special care with Targretin:
- if you have a known hypersensitivity to retinoids (related to vitamin A), suffer from liver disease, have high blood lipids or take medicines which may cause high blood lipids, have uncontrolled diabetes mellitus (sugar diabetes), have had gall bladder or biliary tract disease, or consume excessive amounts of alcohol. If any of these apply you should inform your doctor.

Your fasting blood lipid determinations may have to be performed before therapy is initiated and at weekly intervals afterwards, and then monthly while taking this medicine.

Blood tests to evaluate the function of your liver and thyroid gland and to monitor your red blood cell and white blood cell counts will be obtained before therapy is started and will be monitored during therapy.

Periodic eye exams may be needed if you experience visual difficulties while taking this medicine.

Minimise exposure to sunlight as much as possible and avoid exposure to sun lamps.

Do not take more than 15,000 International Units of vitamin A supplements per day during treatment.

Targretin capsules should not be used in children or adolescents.

Taking Targretin with food and drink:
Targretin should be taken with food. If you regularly consume grapefruit or grapefruit juice, please consult your doctor as these have the potential to alter your body's response to Targretin therapy.

Pregnancy or breast-feeding:
Targretin may be harmful to a developing foetus. DO NOT use Targretin if you are pregnant or breast-feeding. If you are pregnant, thinking of becoming pregnant, or breast-feeding, ask your doctor for more information. If you are capable of becoming pregnant, you must have a pregnancy test within one week before you start therapy, confirming you are not pregnant. You must use effective contraception (birth control) continuously starting one month before beginning therapy until one month after you stop taking Targretin. It is recommended that two reliable forms of contraception be used together. If you are taking a hormonal contraceptive (for example, birth control pills), you should discuss this with your doctor.

If you are male and your partner is pregnant or capable of becoming pregnant, you must use condoms during sexual intercourse while taking bexarotene and for at least one month after the last dose.

Driving and using machines:
It is not known whether Targretin has an effect on your ability to drive a car or operate machinery. If you experience dizziness or problems with your vision during therapy, do not drive or operate machinery.

Important information about some of the ingredients of Targretin:
Butylated hydroxyanisol, an ingredient in Targretin, is an irritant to the eyes, skin, and mucous membranes, therefore the capsules must be swallowed intact.

Taking other medicines:
Before starting treatment, make sure your doctor knows if you are taking medicines (including those not prescribed by your doctor), such as ketoconazole and itraconazole (used against fungal infections), erythromycin, clarithromycin and rifampicin (used against bacterial infections), phenytoin and phenobarbital (used against seizures), gemfibrozil (used to reduce high levels of fats in the blood such as triglycerides and cholesterol), vitamin A supplements, protease inhibitors (used against viral infections), tamoxifen (used against some forms of cancer) or dexamethasone (used for inflammatory conditions). This is important as using more than one medicine at the same time can strengthen or weaken the effect of the medicines.

3. HOW TO TAKE TARGRETIN

Always take Targretin exactly as your doctor tells you to. The doctor will prescribe a suitable dose for you, which is generally 4 to 10 capsules to be taken once daily. Take your prescribed number of capsules at the same time each day with a meal. The capsules can be taken immediately before, during or immediately after the course of the meal, if preferred. The capsules should be swallowed whole and not chewed.

How long you should take Targretin:
Do not stop taking your medication until your doctor advises you to do so. Although some patients have improvement within the first several weeks, most patients require several months or more of treatment to improve.

If you take more Targretin than you should:
If you have taken more than the prescribed dose of Targretin, you must contact your doctor.

If you forget to take Targretin:
If you forget to take one dose, take your daily dose with your next meal on the same day, then take your usual dose as normal, the following day. Do not take a double dose in one day to make up for a missed dose the previous day.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Targretin can have side effects. Tell your doctor as soon as possible if you feel any deterioration in your condition while you are taking Targretin. Sometimes it is necessary to adjust the dose or interrupt treatment. Your doctor will advise you on what to do.

The following side effects were reported in patients with CTCL who were treated with the recommended initial dose of capsules.

Very common:
Low white blood cell count
lowering of thyroid hormones level
Elevation of blood fats (triglycerides and cholesterol)
Skin reactions (Itching, redness, irritation, peeling)
Headache, fatigue, pain

Common:
Low red blood cell count, enlarged lymph nodes, worsening of lymphoma
Thyroid disorder
Elevation of liver enzymes, impaired kidney function, low protein in blood, weight gain
Insomnia, dizziness, reduced skin sensation
Dry eyes, deafness, abnormal sensations of the eye including irritation and heaviness
Swelling of legs and arms
Nausea, diarrhoea, dry mouth, dry lips, loss of appetite, constipation, excess gas, abnormal liver function tests, vomiting
Dry skin, skin disorder, loss of hair, skin ulcer, acne, skin thickening, skin nodule, increased sweating
Joint aches, bone pain, muscle aches
Chills, abdominal pain, allergic reaction, infection

Uncommon:
Blood disorders, eosinophilia, leukocytosis, lymphocytosis, purpura, elevated and decreased numbers of blood platelets
Overactive thyroid
Elevated bilirubin in the blood, impaired kidney function, gout, decreased HDL cholesterol
Agitation, difficulties with balance, depression, increased skin sensation on touching, abnormal nerve sensations, vertigo
Abnormal vision, blurred vision, inflammation of the eye lids, cataract, inflammation of the white part of the eye, lesion of the cornea of the eye, ear disorder, defect in field of vision
Swelling, bleeding, high blood pressure, fast heart rate, visible vein enlargement, dilation of blood vessels
Gastrointestinal disorder, liver failure, inflammation of the pancreas
Changes in hair, herpes simplex, nail disorder, pustular rash, serous drainage, skin discoloration
Muscle weakness
Proteins in urine, abnormal kidney function
Back pain, skin infection, fever, parasitic infection, abnormal laboratory test, disorder of mucous membrane, tumour

Rare fatal side effects are acute inflammation of the pancreas, bleeding in the head, and liver failure.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING TARGRETIN

Always keep this medicine in the closed original pack and out of the reach and sight of children.

Do not store above 30°C. Keep the bottle tightly closed.

Always ensure the container is tightly closed after each dose is removed and store in a dry place.

Do not use after the expiry date stated on the package.

6. FURTHER INFORMATION

For any information about this medical product please contact the local representative of the Marketing Authorisation Holder.

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